DNA

The discovery of DNA 50 years ago changed the pathways of biology more than any other single event of the 20th century. Suddenly, even if not everyone was listening at the time, scientists could visualize the mysterious processes that manufacture life. And one day it could lead to the conquering of human disease.

By John Barbour
Associated Press

As revolutions go, this one was born in a whisper.

Fifty years ago Feb. 1, the scientific

Making a gene map

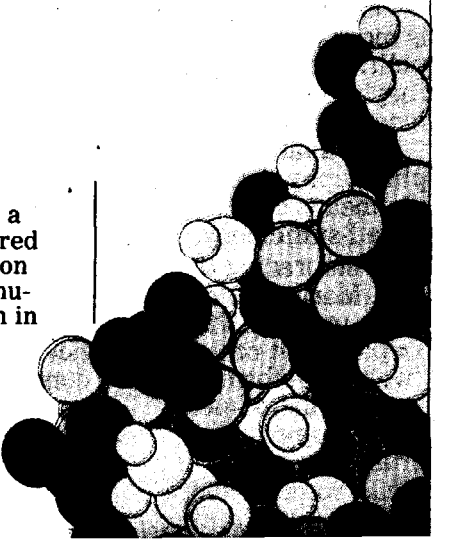
Scientists around the world are in a concerted effort to take the measure of all human genes and have even begun a primitive map of where those genes are in relationship to each other, trying to form the whole genetic picture.

And away from the human body, gene transplants have doubled the life of experimental worms and have fingered three genes that make some bean plants resistant to parasitic rust.

All of these things in the past year.

scientists who published their findings a half-century ago next month, the tortured results of more than a decade of work on bacteria that produced pneumonia in humans, work that frequently found them in their laboratories seven days a week.

Further, it demanded that they fashion the tools of their research so they could pursue their elusive target, as if the smithy had to discover how to dig and smelt iron before he could fashion the horseshoe.



As revolutions go, this one was born in a whisper.

Fifty years ago Feb. 1, the scientific world discovered deoxyribonucleic acid, DNA.

The fact that the carrier of genetic information had been stripped of all its sheltering chemistry was greeted with skepticism and in some cases utter disbelief. It was an event half-noted at the time and little-remembered in the astounding explosion since.

Yet there it was, as the truth gradually sank in: This shadowy substance in the heart of the cell carried the data of everything we would be, our birth certificate and our death certificate all rolled into one, the genetics of all living things, plants and animals: the life force of the planet.

Scientist and philosopher Lewis Thomas, who died last month, put the work into perspective:

"This single discovery opened the way into the biological revolution which continues to transform our view of nature in its most intimate details, and continues to cast up, in its wake, one biotechnology after another for the comprehension and, it can be hoped, the reversal of human disease processes."

Says Nobelist Joshua Lederberg, "The domination by that single theme is enormous. It takes so little imagination to see what needs to be done. Very productive, very important work will come out of there. . . . We're at sort of the point of playing it out."

He compares it to the American and French revolutions, the birth of liberty or the beginning of a search for it.

"All the old ideas are being thrown overboard, the king is dead and we're not saying long live the king, and there's a new era that we're right in the middle of."

Opening new doors

The discovery of DNA changed the pathways of biology more than any other single event of the 20th century. Suddenly, even if not everyone was listening at the time, one could visualize the mysterious processes that manufacture life and hear the multitude of themes and variations, the music of nature.

In the end, it would also open us to the

to parasitic rust.

All of these things in the past year.

And those developments of this year barely scratch the surface.

Last year's Nobel Prize in chemistry was shared by a Californian and a Canadian.

The Canadian, Michael Smith, has a technique that allows scientists to pinpoint a specific place along the genetic code that they want to alter.

The Californian, Kary B. Mullis, invented a process that reproduces millions of cloned segments of DNA within hours, a sort of biological copying machine that can provide more fodder for genetic research in a shorter period of time than old tedious processes.

That event alone led to the "democratization of molecular biology."

Says Lederberg, "With it a single DNA molecule in a messy mixture can be fished out and amplified ad libitum, most importantly at low cost and with simple instruments. High-school students do experiments today that would have been doctoral dissertations 15 years ago.

"The applications range widely, from forensics and diagnosis of genetic disease to the hunt for new viruses and the revival of fossil DNA."

Like in "Jurassic Park"?

Nobel takes note

It came as no surprise to Mullis, who knew his idea, polymerase chain reaction, was a winner and is writing a book on it. He told telephone interviewers when they called with the news that he had won the Nobel Prize that he thought he would go out surfing to wake up and get away from the phone.

All this nonchalance comes from the fact that since Lederberg was awarded his Nobel in 1958, no fewer than 14 Nobels have been awarded for work one way or another connected to DNA and refinements in genetic-research processes.

But this was barely apparent to the three Rockefeller

how to dig and smelt iron before he could fashion the horseshoe.

Even though they received no Nobel Prizes and two of them are now dead, there was a recent plaudit they would have appreciated more. Lewis Thomas introduced a book commemorating their work:

"For better or worse, our lives and those of our children's children are seen as hostages to this relatively

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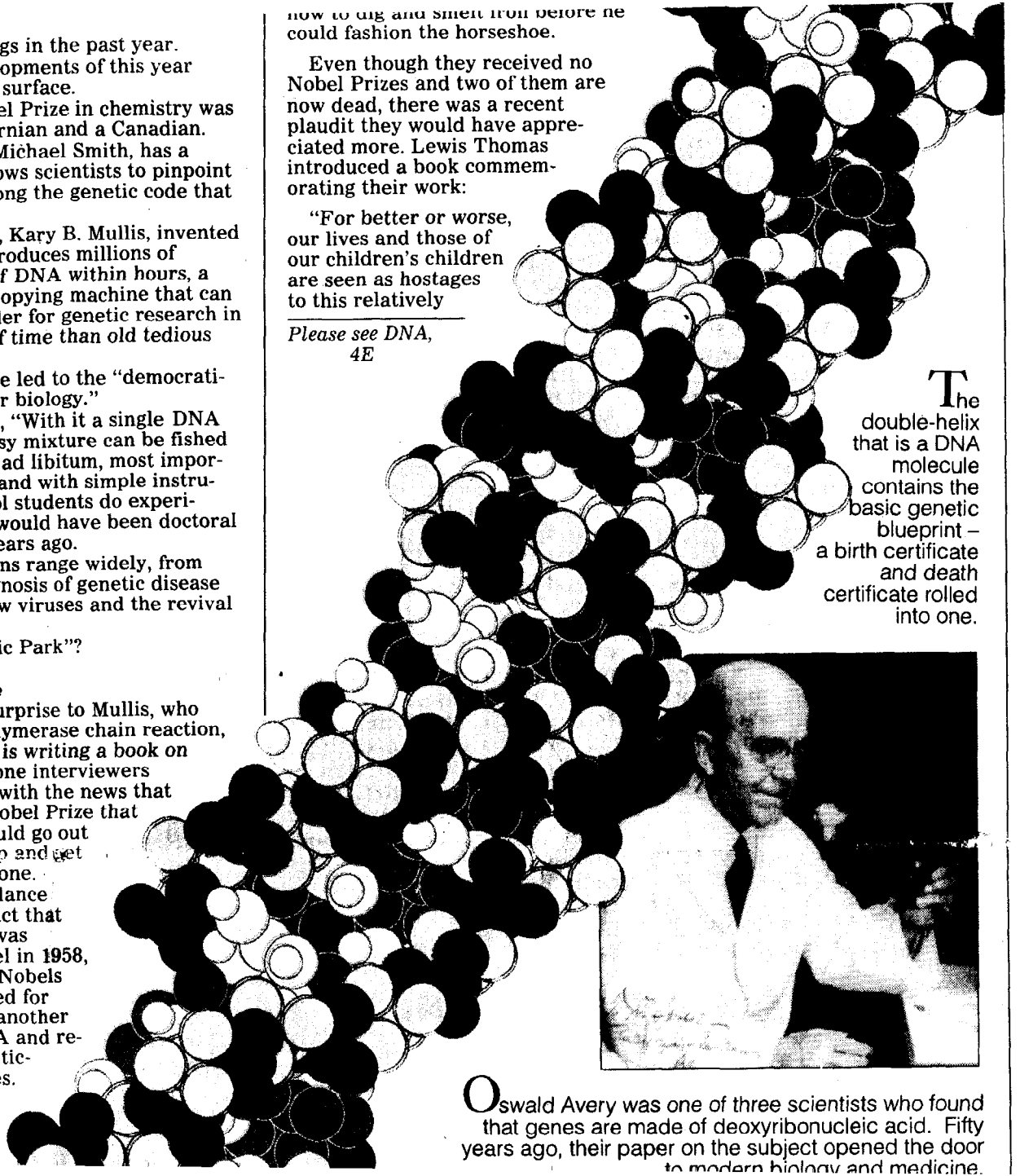


The double-helix that is a DNA molecule contains the basic genetic blueprint – a birth certificate and death certificate rolled into one.

Oswald Avery was one of three scientists who found that genes are made of deoxyribonucleic acid. Fifty years ago, their paper on the subject opened the door to modern biology and medicine.

Now, at what seems the unending crest of the biological revolution, the wave is laden with surfers, and the sea is full of startling ideas.

Genes are used to change the taste of tomatoes and to pin down killers and rapists. Genes are indicted in hereditary diseases from cystic fibrosis to amyotrophic lateral sclerosis, known better as Lou Gehrig's disease.

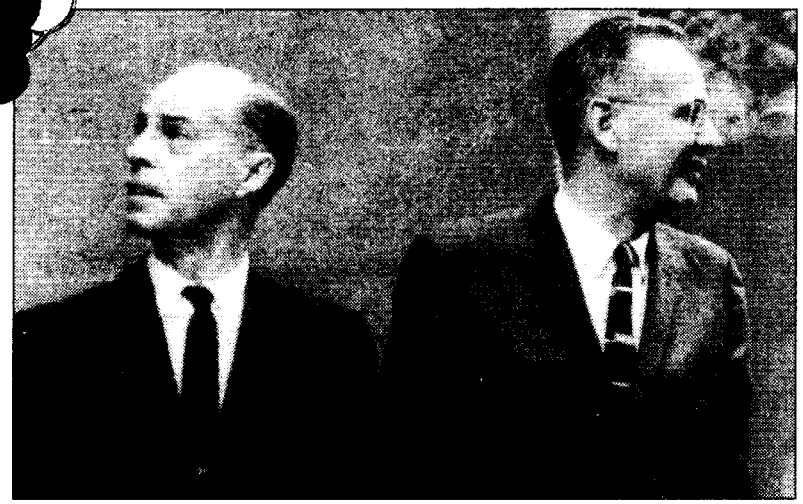
They have the ability to heal themselves or to ignore their deficiencies, thereby causing cancer. They have mobilized other chemicals to do their bidding, and they have proved, so far, vulnerable to the attack of some viruses that need them to survive so they can attack the whole organism, human beings.

Just this year scientists have reported finding genes:

- That predispose some people to hereditary colon cancer.
- That create immune deficiencies, the "Bubble Boy" defect, that strips youngsters of normal defenses, making them susceptible to minor infections that in their cases kill, just as certainly as AIDS patients are bared to the attack of opportunistic infections normal bodies cast off.
- That predispose many young people, notably athletes, to heart failure on the field of play.

University

to modern biology and medicine.



Avery's associates, Colin MacLeod, left, and Maclyn McCarty, co-authored the paper. It was McCarty, the sole survivor of the three, who dedicated a book on "The Transforming Principle," to Avery "who was not inclined to write such a book," and MacLeod, "who ran out of time before he could do it."

50 years after the breakthrough

DNA: *Discovery inspired many to be researchers*

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new way (the scientific way) of looking at and into nature, a method of thinking and working that had its beginnings only a few centuries ago and now dominates all human commerce."

Many hard at work

Today, an incredible number of scientists are compiling DNA's dictionary of life, mapping the entire human genome, all of the information that predicates what we, in all our racial configurations, will become, and indeed how we can manipulate that information to extend or even better our lives.

Lederberg, former president of Rockefeller University, says, "My scientific career spans that interval. That paper came out on Feb. 1, 1944. I remember it. I was just beginning my research work at Columbia University at the time, and it shaped my career. I read it and I said, in today's language, molecular biology is on its way. I want to be a part of it. And I have been."

So it was he won his Nobel. The Rockefeller work inspired him to pursue the largely unknown genetic processes in bacteria, genetic recombination, crossing, mapping and "all the rest of it. And that worked like a charm. It worked almost overnight. That's why my papers came out barely two years after Avery, MacLeod, McCarty on the pneumococcus."

Oswald Avery, a scholarly man of barely 100 pounds, head of the laboratory, and Colin Munro MacLeod, a tall man with a strong sense of perseverance, are both dead. Surviving is Maclyn McCarty, who dedicated a book on "The Transforming Principle" to Avery, "who was not inclined to write such a book," and MacLeod, "who ran out of time before he could do it."

Even more remarkable was the incredibly primitive equipment McCarty and the team worked with. At one point, McCarty says, they needed a centrifuge and fashioned one from a milk separator borrowed from a dairy. Trouble was it filled the laboratory air with the pneumonia bacteria they were working with and a containment vessel had to be built around it.

No one ever got pneumonia, McCarty says, although one technician

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> **— Joshua Lederberg**
> **Nobel Prize winner**

people who had sickle-cell anemia, with the consequence that many Mediterranean and African people survived exposure to the epidemics of disease only to become heir to the debilities of the anemia, passing it on to new generations.

Now, genetic counseling tells prospective parents of disabled fetuses in time to abort birth. In more advanced cases of genetically ordered disease, doctors have terminated life when the mere act of breathing and living became too much of a burden, as in cystic fibrosis. Yet mercy killing, euthanasia, is an outcome that society and its courts have wrestled with for years.

With greater genetic surveillance, there will be not only the balance between life and death, but also between half-life and death.

Now, scientists have learned how to transplant stretches of genes into mice; the genes are then passed on to mouse offspring. They have used yeast cells as harbors for artificial chromosomes that can then be inserted into mice that then reproduce with the chromosomes intact.

Issues of morality

What is the use of all this? More than just building animal factories to toy with genes?

It can become a tool to trim genetic material to isolate a new gene. It can become a tool for producing monoclonal antibodies that can be used safely to enhance disabled immune systems. It can

No one ever got pneumonia, McCarty says, although one technician carried dormant bacteria in his throat cultures. Avery himself, McCarty remembers, recovering from surgery for hyperthyroidism, developed a fever and confided to the intern, "Wouldn't it be the irony of fate if that little bug got me in the end."

Lederberg says the very nature of their discovery preset the agenda for future research "in a way we've just never seen before."

People talk about the Human Genome Project and the sequencing of it from end to end as The Holy Grail, Lederberg says, but he adds, "I think we have to go in much greater depth in sequencing one gene at a time (mapping its personal details). That's really the message. There are 100,000 genes, give or take a factor of two. We know about a thousand of them today. There's a century of work just completing that exploration and it's got to be done, and it's easy to do. . . . There's no mystery of what needs to be done next. At least we've identified the mystery.

"Now that could be overturned. There could be findings that we have no glimmer of beyond that," but betting his track record, he doesn't think so. "Right now this looms so large and our landscape is just so dominated by the completion of this exploration that it's very hard to look beyond it."

Issues of humanity

Lewis Thomas looked at "this most scientific of centuries" with a kindly eye, merging the world of insects such as termites and the maternal mimosa beetle with the affairs of humankind. Humans, beyond all of nature's programmed species, have most often to deal with change — and what greater change than learning what is your basic engine of life and the ability to manipulate it.

"Although each new century differs in fundamental ways from all preceding periods of history," he wrote in his introduction to McCarty's book, "the 20th century seems unique for the overwhelming scale of the transformation of human life affecting people everywhere . . ."

There have been myriad attempts to design human life. Hitler's brutal matching of mates to create a master race is only one of the bizarre outgrowths of this kind of thinking.

Nature's solutions may not always be wise when it abbreviates lives that are genetically vulnerable.

But its solutions are inevitable. The malarial parasite could not attack the crippled blood cells of that can be used safely to enhance disabled immune systems. It can be used to find those mystery chemicals that turn a gene on or off.

Perhaps the expectations rising from the isolation of DNA and its explication were too great. Thomas remembered, "We called it a biological revolution when the fantastic geometry of the DNA molecule was exposed to public view and the linear language of genetics was decoded. For a while things seemed simple and clear; the cell was a neat little machine, a mechanical device ready for taking to pieces and reassembling, like a tiny watch."

But, he said in one of his later books, it has become "imponderably complex," no longer a set of instructions on a tape. There are stretches of nonsense, stretches of aberrant behavior where the genes won't stand still; even the skin of the cell becomes a mosaic of signals, "an organ in itself."

"Cells communicate with one another, like bees in a hive, regulate one another."

So anyone who expected easy answers had best look again.

For centuries, animal husbanders tinkered with the lines of their livestock to build better breeds. Farmers cross-pollinated plants to build a better potato or disease-free wheat.

Hitler's men had the same idea with human beings, using sterilization, extermination and selective breeding in a vain attempt to create a master race. What might they have done with gene manipulation?

Man has always sought to govern his future. Even now, some closely bound and sheltered groups that have inbred for years are seeking genetic counseling to break the inherited chain of defective genes.

In the general population samples of amniotic fluid can betray suspected genetic abnormalities and lead to abortions to avoid the burden of saddling a family, or society, with crippled offspring.

Perhaps one day genetic repair may obviate the presumed need for such dire alternatives, including mercy killings.

But those alternatives are still far away, perhaps not so far as they were half a century ago, but still distant.

Fifty years after Avery, MacLeod and McCarty stripped DNA of its mystery and people such as Lederberg and Frances Crick and James Watson — who won a Nobel Prize for discovering the shape of DNA — elucidated it eloquently, the ball is still in the fairway.